

DOCKET NO: 242791US0CONT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
TETSUYA SUGA, ET AL : EXAMINER: BROOKS, KRISTIE
LATRICE.
SERIAL NO: 10/692,684 :
FILED: OCTOBER 27, 2003 : GROUP ART UNIT: 1616
FOR: IMMUNE ACTIVATOR:

DECLARATION UNDER 37 C.F.R. §1.132

COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313

SIR:

Now comes Ko Okumura, M.D., Ph.D., who declares and states:

1. I was formerly a professor in the Department of Immunology, School of Medicine, Juntendo University.
2. I was formerly the President of the Japanese Society for Immunology.
3. I am currently President of Atopy (Allergy) Research Center (Japan).
4. I previously discovered suppressor T cells and frequently published in this area of technology.
5. I am a recognized authority in the field of Immunology.
6. I am being compensated at my regular consulting rate for my time spent in preparing this opinion. I have no financial interest in the outcome of the examination of this application. I am under a commission agreement with AJINOMOTO PHARMACEUTICALS

Co., Ltd. (which is a subsidiary of AJINOMOTO Co., Inc.) as an advisor (advice on research and development, and academic support) regarding products (such as pharmaceuticals) of AJINOMOTO PHARMACEUTICALS Co., Ltd.

7. At the request of Ajinomoto Co., Inc., the assignee of the above-identified application, I have reviewed:

- a. Declaration under 37 C.F.R. §1.132 executed by Yasuyo Suga filed on September 23, 2009;
- b. Declaration under 37 C.F.R. §1.132 executed by Yasuyo Suga filed on September 27, 2010;
- c. Suga et al., Biotherapy. 19(3):273-278, 2005;
- d. Uchiyama et al (US 2002/0119164);
- e. Kropf et al (US 6,858,214); and
- f. Desai et al, Pharmaceutical Research, vol. 13 (12), 1996, 1838-1845.

8. Based on my review of the foregoing, I provide the following comments on the state of the relevant art as it pertains to the invention of the Application.

9. It is my opinion that the results demonstrated in the Declaration under 37 C.F.R. §1.132 executed by Yasuyo Suga filed on September 23, 2009, are unexpected at least for the reasons stated in the Declaration under 37 C.F.R. §1.132 executed by Yasuyo Suga filed on September 27, 2010.

10. Specifically, it is my opinion that there is no direct relation between absorbability and the medical effect. Thus, the results of the present invention as demonstrated in the

Declaration under 37 C.F.R. §1.132 executed by Yasuyo Suga filed on September 23, 2009, are unexpected. My opinion is further reinforced by Suga et al., *Biotherapy*. 19(3):273-278, 2005.

Specifically, Suga et al., *Biotherapy*. 19(3):273-278, 2005 discloses the comparison of the anti-tumor effects between three different particle size samples (solutions):

(a) L-LNT: the solution obtained by subjecting Lentinan solution to centrifugation (8,000G, 10 min), and then suspending the precipitation in distilled water again (in which the mean particle size of the solution is approximately 130 μm);

(b) S-LNT: the supernatant obtained through centrifugation (8,000G, 10 min) (in which the mean particle size is below the possible range of measurement (i.e., not more than 0.01 μm);
and

(c) M-LNT: the solution obtained by subjecting Lentinan solution to high-pressure homogenized treatment after mixing the solution with a Lecitin solution (in which the mean particle size of the solution is approximately 0.1 μm). (See Figure 1)

As shown in Figure 4, in case of the intraperitoneal administration, three different particle size samples show the same level of anti-tumor effects.

However, in case of oral administration, only M-LNT shows significant anti-tumor effects. Therefore, in case of oral administration, anti-tumor effects are not shown when the particle size becomes too small. Thus, in case of the oral administration, even if the particle size is decreased, the effects are not necessarily improved, and a correlation between the particle size and the effects can not be predicted and would not have been expected.

11. I declare further that all statements made of my own knowledge are true and that all

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statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

12. Further Declarant saith not.

Ko Okumura
Ko Okumura, M.D., Ph.D.

April 7, 2011
Date